

# The usefulness of plasmapheresis in acute pancreatitis due to hypertriglyceridemia: A case report

Gina Sofía Montaña-Padilla, MD,<sup>1\*</sup> Alejandro Concha-Mejía, MD,<sup>2</sup> Reinaldo A. Rincón-Sánchez, MD,<sup>2</sup> Karen Rodríguez-Ruiz, MD.<sup>3</sup>

1. Critical and Intensive Care Resident at the Universidad de la Sabana and Fundación Clínica Shaio in Bogotá, Colombia
2. Specialists in Internal Medicine, Gastroenterology and Digestive Endoscopy at Fundación Clínica Shaio in Bogotá, Colombia
3. Internal Medicine at Fundación Clínica Shaio in Bogotá, Colombia

\*Correspondence: Gina Sofía Montaña-Padilla, MD, [deogratias10@hotmail.com](mailto:deogratias10@hotmail.com)

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## Abstract

**Introduction:** Globally, acute pancreatitis has a high incidence and a large. Among its numerous causes, the most frequent are obstructions of the bile duct, alcohol consumption and hypertriglyceridemia (triglyceride serum levels higher than 1000 mg/dL). Hypertriglyceridemia accounts for 1% to 7% of the total cases.

**Methodology:** We present a case of acute pancreatitis secondary to severe hypertriglyceridemia which was managed with plasmapheresis. We include a review of the literature on the conditions, indications and advantages of this therapeutic strategy. **Conclusions:** In selected cases, plasmapheresis is a safe and effective management strategy for patients with acute pancreatitis secondary to severe hypertriglyceridemia.

## Keywords

Pancreatitis, hypertriglyceridemia, plasmapheresis.

## INTRODUCTION

The incidence and impact of acute pancreatitis are high worldwide. (1) It has multiple causes, but the most frequent are bile duct obstruction, alcohol consumption and hypertriglyceridemia. The last, understood as serum triglyceride levels over 1,000 mg/dL, accounts for 1% to 7% of all cases.

The signs and symptoms of acute pancreatitis due to hypertriglyceridemia are similar to acute pancreatitis due to other causes. Possible pathophysiological mechanisms include congenital disorders, metabolic alterations, and certain medications. Within this context, dietary restrictions are still a key element of management of acute pancreatitis to which other strategies such as the use of heparin or insulin can be added. These substances allow the release and activation of lipoprotein lipase (LPL) to promote lipid degradation which favors the discovery of plasma exchange options as a screening tool.

We present a case that was diagnosed at a fourth level of complexity hospital in Bogotá. We describe the patient's clinical evolution and management used and provide a brief review of the literature regarding this diagnosis.

## CLINICAL CASE

This patient was a 32-year-old man who had had an appendectomy but had no other important precedents. He was admitted on October 12, 2016 after two days of constant abdominal pain of an intensity of 8/10 and a feeling of heaviness in the hypogastrium, right hypochondrium and left hypochondrium.

The intensity of pain progressively increased to 10/10 degree, did not radiate, and was associated with abdominal distention related to copious intake of food (mainly flour-based). The patient said that he only drank alcohol once a month (only beer) and did not become. The most recent time had been five days before onset of pain on October 5, 2016.

Upon admission, the patient manifested persistent abdominal pain which reached an intensity of 7/10. He was dehydrated, his heart rate (HR) was 89 bpm, his respiratory rate (RR) was 20 rpm, his blood oxygen saturation was 90%, his blood pressure (BP) was 120/64 mm Hg, and his temperature was 36.4 ° C (**Table 1**).

**Table 1.** Results from tests performed at admission

<b>Total abdominal ultrasound</b>	Performance and interpretation were markedly limited by interposition of gas and voluntary abdominal defense of the patient. Moderate hepatic steatosis. Retroperitoneum not assessable. An adequate evaluation of the gallbladder neck was not possible.
<b>Lipid profile</b>	Total cholesterol: 301 mg/dL; HDL: 22 mg/dL; LDL: due to triglycerides result could not be calculated. Triglycerides: 2.50 mg/dL
<b>Hepatic profile</b>	Total bilirubin: 0.84 mg/dL; direct: 0.00 mg/dL; indirect: 0.34 mg/dL; delta: 0.50 mg/dL; alkaline phosphatase: 152 UL; serum amylase: 2.26 UL
<b>Arterial gases</b>	FiO2: 0.21; pH: 7.41; PaCO2: 31.6 mm Hg; PaO2: 67.2 mm Hg; HCO3: 19.7 mEq/L; BE: -3.7; oxygen saturation: 92.5%; glucose: 88 mg/dL; lactate: 0.71 mmol/L
<b>Electrolytes</b>	Calcium: 8.7 mg/dL; chlorine: 104 mEq/L; potassium: 3.9 mEq/L; sodium: 139 mEq/L
<b>Kidney function</b>	Creatinine: 0.8 mg/dL; BUN: 13 mg/dL
<b>Complete blood count</b>	Leukocytes: 9,900 per mm <sup>3</sup> ; neutrophils: 70%; lymphocytes: 19%; erythrocytes: 5.2; hemoglobin: 16.5 g/dL; hematocrit: 44.4%; platelets: 270,000 per mm <sup>3</sup>

HDL: high-density lipoprotein; LDL: low-density lipoprotein; FiO2: fraction of inspired oxygen; PaCO2: partial pressure of carbon dioxide in arterial blood; PaO2: partial pressure of oxygen; HCO3: bicarbonate; BE: base excess; BUN: blood urea nitrogen.

On physical examination, the patient' oral mucosa was dry and his bowel sounds' tone and frequency were normal. On palpation his abdomen was soft and depressible. He experienced intense pain in the upper hemiabdomen, predominantly in the right upper quadrant. Murphy's sign could not be assessed by voluntary defense. There were no signs of peritoneal irritation.

Given the clinical suspicion of acute pancreatitis, his serum amylase level was measured and found to be 2.26 UL. A triglyceride test then found severe hypertriglyceridemia.

Given that his APACHE II score was 1 with a predicted mortality of 0%, we considered that he had mild acute pancreatitis due to severe hypertriglyceridemia. For this reason, we prescribed plasmapheresis and insulin infusion.

The patient was transferred to the intensive care unit (ICU). Upon admittance his HR was 73 bpm, his RR was 21 bpm, his BP was 114/73 mm Hg, and his blood glucose was 70 mg/dL. He did not require vasopressor or inotropic support, and no significant changes were found in the physical examination.

The intensive care unit decided not to start insulin infusion since there was a borderline blood glucose test. Follow-up tests were requested before performance of plasmapheresis as a second therapeutic alternative (**Table 2**).

**Table 2.** Results of tests performed prior to plasmapheresis

<b>Hepatic profile</b>	Total bilirubin: 0.84 mg/dL; direct: 0.00 mg/dL; indirect: 0.34 mg/dL; delta: 0.50 mg/dL; alkaline phosphatase: 152 UL
<b>Electrolytes</b>	Calcium: 8.5 mg/dL; magnesium: 1.5 mg/dL; potassium: 3.7 mEq/L; sodium: 138 mEq/L
<b>Kidney function</b>	Creatinine: 0.7 mg/dL; BUN: 9 mg/dL
<b>Complete blood count</b>	Leukocytes: 9,600 per mm <sup>3</sup> ; neutrophils: 69%; lymphocytes: 24%; erythrocytes: 4,640 per mm <sup>3</sup> ; hemoglobin: 14.2 g/dL; hematocrit: 39.7%; platelets: 211,000 per mm <sup>3</sup>

BUN: blood urea nitrogen

Finally, plasmapheresis was performed on the patient's date of admission (start: 8:00 p.m., end: 10:30 p.m.) through the peripheral route. There were no complications and his triglyceride level subsequently decreased significantly (**Table 3**).

**Table 3.** Follow-up tests during hospital stay

<b>Electrolytes</b>	Potassium: 3.8 mEq/L; sodium: 138 mEq/L; chlorine 103 mEq/L
<b>Triglycerides</b>	780 mg/dL
<b>Total cholesterol</b>	329 mg/dL
<b>Kidney function</b>	Creatinine: 0.6 mg/dL; BUN: 7 mg/dL
<b>Complete blood count</b>	Leukocytes: 5,500 per mm <sup>3</sup> ; neutrophils: 40%; lymphocytes: 44%; erythrocytes: 4,900 per mm <sup>3</sup> ; hemoglobin: 14.8 g/dL; hematocrit: 42.7%; platelets: 203,000 per mm <sup>3</sup>

BUN: blood urea nitrogen

On the following day, a second planned plasmapheresis was suspended since the first session was successful.

The patient's control triglyceride level was less than 1,000 (841), and there were no signs of abdominal pain or fever peaks. Thus, the patient was hemodynamically stable and without signs of a systemic inflammatory response.

Considering his clinical evolution, oral feeding was begun, his analgesia was adjusted, and his intravenous fluid intake was reduced. Management with oral fibrates (fenofibrate 200 mgd) was started to continue addressing his hypertriglyceridemia.

The patient was transferred to the general hospital floor, and clinical management continued. He remained asymptomatic and showed acceptable tolerance to oral feeding without signs of a systemic inflammatory response and without need for supplemental oxygen. Follow-up tests indicated a favorable pharmacological response, so we decided to discharge him.

## LITERATURE REVIEW

### General Considerations

Acute pancreatitis is an entity with a high incidence and impact worldwide (1). This pathology has multiple causes and the most frequent are bile duct obstruction and hypertriglyceridemia, which is understood as those serum triglyceride levels > 1000 mg/dL, whose scenario represents between 1 and 7% of all patients. cases.

### Clinical Manifestations

Hypertriglyceridemia is very similar to the other etiologies of pancreatitis. After eating food patients usually present sudden and severe pain in the upper third of the abdomen, accompanied by nausea, hyporexia, and emesis. (2)

More specific but less frequent symptoms include chronic hyperlipidemia, eruptive xanthomas on the extensor surfaces of the extremities, and hepatosplenomegaly due to fatty infiltration in the liver. (3, 4)

In this sense, paraclinical diagnosis with respect to biliary etiology differs only in the serum finding of triglyceride levels exceeding 1,000 mg/dL. (4)

The natural history of this condition shows a decrease in serum triglyceride levels in the first 72 hours after fasting starts. This occurs due to the decrease in the supply and absorption of chylomicrons which was observed in our patient although the result may have been influenced to a large extent by treatment. (5)

### Pathophysiology

Triglycerides constitute one of the most important components of chylomicrons and very low intensity lipoproteins

(Very Low Density Lipoprotein, VLDL). (6) Their main source is derived from diet and they are absorbed through the intestinal epithelium to join preformed chylomicrons and pass through the basolateral membrane.

From there they are conducted to the lymphatic vessels and then reach the venous circulation through the thoracic duct. (7) In this way, they acquire apolipoprotein C-II, an essential cofactor for LPL. (8) Thus, chylomicrons and VLDL are transported to muscle and adipose tissue where they are metabolized by LPL in accordance with systemic energy demand.

It has been proposed that serum triglyceride levels over 100 mg/dL indicate exocrine overstimulation despite other blood test results. (9) This implies increased release of pancreatic lipase which, like LPL, breaks down triglycerides into fatty acids and acylglycerols. These lipids are toxic to acinar cells and pancreatic tissues and generate an inflammatory environment that is harmful to tissue viability. (10)

### Etiology

Hypertriglyceridemia has been classified into primary and secondary. Primary hypertriglyceridemia is caused by a group of hereditary metabolic disorders that predispose alterations in the metabolism of fatty acids. (11) Secondary hypertriglyceridemia is possibly the causal mechanism of our patient's condition. Diabetes mellitus is included in this group since limited secretion or lack of effectiveness of insulin has been shown to be related to less synthesis of LPL which facilitates the accumulation of triglycerides. (12)

Secondary causes include alcohol consumption which compromises lipid metabolism and absorption, and drugs such as estrogens and tamoxifen which induce insulin resistance and favor synthesis of lipoproteins such as VLDL. (13, 14) This also occurs during pregnancy when the action of LPL and liver lipases decreases leading subsequently to increases in serum triglyceride levels (Table 4). (15)

**Table 4.** Causes of hypertriglyceridemia

<b>Primary hypertriglyceridemia</b>	Genetic: Types I, IV, and V in the Fredrickson classification
<b>Secondary hypertriglyceridemia</b>	Diet: excess alcohol, weight gain. Medications: exogenous estrogens, tamoxifen, retinoid, thiazides, β blockers, propofol. Alterations in metabolism: diabetes, chronic kidney disease, hypothyroidism.

### Treatment

Initial management of hypertriglyceridemic pancreatitis is similar to acute pancreatitis with other causes. It includes

fluid resuscitation, analgesic management, and bowel rest. However, in cases of hypertriglyceridemic pancreatitis, the serum triglyceride level should be rapidly lowered simultaneous to the general therapeutic approach. This facilitates symptom resolution and reduces the risk of recurrence. (16)

Administration of insulin is one treatment option. (17) It promotes storage of glucose and fatty acids and stimulates the hepatic production of apolipoprotein B100, rich in VLDL1, and the intestinal production of VLDL2 by action of apolipoprotein B48. The latter increases hydrolysis of triglycerides by acting as a catalyst for LPL. (18)

Although no protocol has yet made insulin administration standard treatment of acute pancreatitis due to hypertriglyceridemia, intravenous administration of crystalline insulin at a dose of 0.1-0.4 U/kg/h has been proposed. Euglycemia should be maintained by simultaneous infusion of dextrose. (19)

Heparin is another option which enhances the activity of LPL and initially accelerates metabolism of triglycerides. (20) This happens because LPL breaks down over time and is eliminated through the liver. Therefore, the administration of intermittent doses of low molecular weight heparin or unfractionated heparin (bolus of 18 U/kg and repeat doses at 4-6 h) is recommended. (21) No significant differences have been seen between the two.

Octreotide should also be considered. (22) It is a somatostatin analog which inhibits gastrointestinal secretion of insulin, glucagon, gastrin, cholecystokinin, vasoactive intestinal peptide, pepsin, secretin and pancreatic exocrine enzymes. Octreotide acts through SSTR4 and SSTR5 receptors and on acinar cells from which their beneficial interference in the described pathophysiological cascade can be inferred. (23)

As one of the final options, especially when serum triglyceride levels are over 1000 mg/dL, plasmapheresis should be considered. (24) Plasmapheresis works through two mechanisms. The first one is related to mechanical sweeping of triglycerides while the second is the addition of LPL and apolipoproteins from the fresh frozen plasma of the donor. Two to three liters of plasma are replaced by a central venous catheter (usually internal jugular) and this volume is replaced with 5% albumin, associated with fresh frozen plasma.

Some authors have described a decrease of up to 66.3% (in the case, 68.8%) despite no clear impact on APACHE II severity scores or hospital stays. (25, 26) For this reason, the American Society for Apheresis (ASFA) has proposed plasmapheresis within grade III recommendations for management of this entity. (27)

The most frequent complications secondary to plasmapheresis are urticaria (0.7-12%), hypotension (0.4-4.2%),

muscle cramps (0.4-2.5%) and inconveniences related to central vascular access (0.08-4%). (28)

Once the acute episode has been resolved, long term treatment of hypertriglyceridemia should begin by setting levels as close to normal as possible (<1450 mg/dL). To do this, the patient must perform aerobic physical exercise at least three times a week, follow a low-fat diet, and use three classes of medications (alone or in combination).

The first are fibrates which reduce triglyceride levels 30 to 50% and facilitate oxidation of fatty acids. (28) In addition, they increase synthesis of LPL and decrease expression of apolipoprotein C-III which translates into decreased triglyceride production. Adverse effects include gastrointestinal intolerance and the formation of cholesterol gallstones.

On the other hand, doses of 500-2000 mg/d niacin provide cardiovascular protection and reduce triglycerides by 10 to 30%. (29) It increases high-density lipoprotein (HDL) cholesterol by 10 to 40% and lowers low-density lipoprotein (LDL) by about 5 to 20%. The most common adverse reaction is dermatitis, which usually occurs within the first 60 minutes after ingestion.

Meanwhile, omega-3 acids (docosahexaenoic acid [DHA]) and eicosapentaenoic acid (EPA) decrease triglyceride levels in proportion to their dose. (30) Three to five g of EPA associated with DHA reduce this type of fat 20 to 50% while simultaneously increasing HDL by about 5%. These acids are especially useful when fibrates are contraindicated (**Table 5**). (30-32)

**Table 5.** Long-term drug treatment

<b>Duration:</b> indefinite
Fibrates: fenofibrate, bezafibrate (400 mg/d), ciprofibrate (100 mg/d). Niacin: 500-2000 mg/d (maximum dose 2000 mg/d). Omega-3 fatty acids: 3-5 g postprandial.
<b>Expected time of onset of effect:</b> 6 weeks

## CONCLUSION

Acute pancreatitis caused by hypertriglyceridemia is rare. Timely identification of the etiological mechanism is important for facilitating correction of the pathophysiological cascade. Management is based especially on hydrolysis of triglycerides through the action of insulin or the sweep and supplement effect of LPL that originates from plasmapheresis. Initial management is followed by oral administration of agents that promote oxidation of fatty acids to achieve symptomatic remission and reduction in the risk of recurrence.



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